Regardless of the answers to these concerns, it is sobering to consider Reich’s argument that there is not any one single agent and that there is not one discrete immunologic defect that causes sarcoidosis. For sarcoidosis to occur, patients may have to experience a specific interaction between one or several exposures and one or several abnormal immunologic responses. If this model is correct, it will be extremely difficult to prove. And perhaps the absence of proof for any etiology of sarcoidosis may be the most compelling argument supporting Reich’s hypothesis. We still have not figured out the cause of sarcoidosis perhaps because there is not just one cause.

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Treatment of Pulmonary Arterial Hypertension
A Step Forward

No great improvements in the lot of mankind are possible, until a great change takes place in the fundamental constitution of their modes of thought.

John Stuart Mill, 1873

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of the pulmonary vascular bed. If untreated, PAH progresses to
ET-1 synthesis and is responsible for clearance of endothelial cells. Additionally, ET-B indirectly modulates vasodilation via ET-B receptors located on vascular smooth muscles. ET-1 causes vasoconstrictor effects; however, blockade of both ET-A and ET-B is required to inhibit the effects of ET-1 on pulmonary circulation. Recent discoveries have identified a role for transforming growth factors (transforming growth factor β) and vascular endothelial cell growth factor (VEGF) in the pathogenesis of PH. VEGF blockade produces PH and pulmonary vascular remodeling, explaining beneficial effects of prostaglandins, which provoke VEGF production.6 Mutations in the bone morphogenetic protein receptor type II have been reported in patients with familial and sporadic PPH.7 Dysfunction of this receptor may contribute to proliferation of smooth-muscle cells and partake in pathogenesis of PAH.

Therapy for PAH previously consisted of calcium-channel blockers that resulted in beneficial response in approximately 20% of patients, and detrimental effects in nonresponders. The responders are identified when vasoreactivity (hemodynamic improvement) is demonstrated during acute vasodilator trial.8 Continuous IV epoprostenol therapy improved functional capacity and survival irrespective of vasoreactivity, and became the first-line therapy for patients with PAH who were symptomatic equivalent to New York Heart Association (NYHA) functional class III and class IV.9 Prostaglandins are vasodilators with antiplatelet effects and achieve anti-inflammatory, antifibrotic, and antiproliferative effects. Difficulties with drug administration, high costs, and undesirable side effects of epoprostenol necessitated the development of prostacyclin analogues administered by continuous subcutaneous infusion, orally or by intermittent inhalation.10,11 Treprostinil administered by continuous subcutaneous infusion is presently available in the United States. Oral beraprost and inhaled iloprost, in placebo-controlled clinical trials,12,13 appear promising for patients in NYHA class II and class III. Inhaled iloprost has the disadvantage of short duration of action and requires 6 to 12 inhalations per day.

Phosphodiesterase inhibitors increase the intracellular concentration of cyclic guanosine monophosphate and cyclic adenosine monophosphate, and have shown to possess vasodilatory properties on pulmonary circulation. Beneficial effects of sildenafil have been reported in published case reports.14 Inhalation of nitric oxide, a vasodilator of pulmonary circulation, has been shown to improve exercise capacity in patients with PAH. Oral L-arginine, a nitric oxide donor, decreased pulmonary vascular resistance, and improved circulation and exercise capacity in patients with PAH.15 However, the experience with sildenafil and L-arginine is limited; further clinical trials are required to document efficacy and safety of these drugs.

Inhibiting effects of ET by ET-receptor blockade is a novel and effective therapy for patients with PAH. Bosentan, an orally active nonpeptide, is a...
This study established that long-term administration of bosentan is safe and efficacious in the treatment of PAH.

In the absence of long-term data comparing different treatments, the choice of therapy will depend on clinical experience, patient preferences, and costs. All patients should be treated with oral anticoagulation unless otherwise contraindicated. In patients with mild-to-moderate PAH who belong to NYHA class I and class II, and who demonstrate vasoreactivity on acute vasodilator trial, calcium-channel blockers remain the treatment of choice. Nonresponders of NYHA class II who are in stable condition may be closely observed; if therapy is required, oral beraprost or bosentan are the most appropriate choices. The first-line treatment for patients in NYHA class III could be either oral/inhaled/subcutaneous prostaglandin or ET antagonist. IV prostacyclin should be administered if deterioration ensues. For most patients with severe PAH (NYHA class IV), the treatment of choice is IV prostacyclin. Therapy with ET antagonist, however, can be initiated in patients with stable clinical status under careful supervision. Inhaled prostacyclin has been reported to be effective in the treatment of severe PAH and is a reasonable alternative, if available, and in those who acquire severe hypotension receiving IV therapy.

In the future, clinical trials will help define a place for various agents in the treatment of PAH. Long-term studies will also address the issues of survival, quality of life, side effects, and costs with a range of therapeutic agents. Another promising approach is combining two agents with diverse pharmacologic actions; such clinical studies are currently underway. Finally, reversal of PH and regression of histologic changes in pulmonary circulation may potentially become a therapeutic reality.

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Death in the ICU

Feelings of Those Left Behind

Heyland and colleagues deserve congratulations for their study, “Dying in the Intensive Care Unit: Perspectives of Family Members” in this issue of CHEST (see page 392). In this multicenter study conducted at tertiary care centers, the authors documented the fact that 83% of family members were satisfied with the care that their loved ones received. The authors credit the good communications, decision making, respect, and compassion shown in the care of patients and their families for these results. The experience of the American investigators has been much less satisfactory than their Canadian counterparts. Lynn and colleagues1 reported in 1997 on the larger Study To Understand Prognosis and Preferences for Outcomes and Risks of Treatment (SUPPORT) and the Hospitalized Elderly Longitudinal Project. They were less sanguine about their findings. On interviewing surrogates of the elderly or seriously ill patients who had died within a year of the hospitalization, they found that almost 60% of patients would have preferred comfort care. They also discovered that in 10% of the cases, care was contrary to the preferred approach. The 11% rate of attempted resuscitation was almost four times higher than the 3% rate in the study by Heyland et al. The SUPPORT study revealed that one third of the patients were in unexpected pain at the time of death vs good pain management found in 90% of Canadian patients.

Lynn et al referred to the only substantial study for their study, “Dying in the Intensive Care Unit: Perspectives of Family Members” in this issue of CHEST (see page 392). In this multicenter study conducted at tertiary care centers, the authors documented the fact that 83% of family members were satisfied with the care that their loved ones received. The authors credit the good communications, decision making, respect, and compassion shown in the care of patients and their families for these results. The experience of the American investigators has been much less satisfactory than their Canadian counterparts. Lynn and colleagues1 reported in 1997 on the larger Study To Understand Prognosis and Preferences for Outcomes and Risks of Treatment (SUPPORT) and the Hospitalized Elderly Longitudinal Project. They were less sanguine about their findings. On interviewing surrogates of the elderly or seriously ill patients who had died within a year of the hospitalization, they found that almost 60% of patients would have preferred comfort care. They also discovered that in 10% of the cases, care was contrary to the preferred approach. The 11% rate of attempted resuscitation was almost four times higher than the 3% rate in the study by Heyland et al. The SUPPORT study revealed that one third of the patients were in unexpected pain at the time of death vs good pain management found in 90% of Canadian patients.

Lynn et al referred to the only substantial study published by legendary William Osler in 1908. Reporting on 486 deaths at Johns Hopkins, he was convinced that only 90 patients felt pain at the time of death. Unfortunately, Osler’s own end was not that free of pain! Nuland,2 through Osler’s own words, provides a poignant description of the 6 weeks of his enduring sharp pleuritic pain and bouts of coughing. In those primitive days, he had undergone two operations to drain empyema under general anesthesia. Two weeks later when he died,